ENVIRON

October 4, 2010

Dr. Ellen Mantus
Senior Program Officer for Risk Analysis
National Academy of Sciences
500 Fifth St. N.W.
Washington, D.C. 20001
Email: emantus@nas.edu

RE: **Lack of Evidence of Biological Plausibility for a Causal Association Between Exposure to Formaldehyde and the Incidence of or Mortality from Myeloid Leukemia**

Dear Members of the NAS Committee:

On behalf of Hexion Specialty Chemicals, Inc., ENVIRON International Corporation has conducted a review of the USEPA's Draft IRIS Assessment for Formaldehyde, which included an evaluation of the evidence for the biological plausibility of a causal association between exposure to formaldehyde and myeloid leukemia. As indicated in the text of this letter, review of the evidence indicates that such a causal association is not biologically plausible because of: 1) a lack of evidence of transport of exogenous formaldehyde beyond the portal of entry; 2) a lack of concordance with toxicity produced by other known leukemogens; and 3) a lack of evidence to support the proposed mode(s) of action (MOA). Further, USEPA's proposed unit risk factor (USEPA 2010) would result in an estimated allowable air concentration (at a 1×10^{-6} extra lifetime cancer risk) that is a **biologically implausible value**[1] - i.e., this concentration is orders of magnitude below that which is normally exhaled as a result of endogenous processes.

A. Lack of Evidence of Transport of Exogenous Formaldehyde Beyond the Portal of Entry

The proposed mechanisms by which formaldehyde may promote leukemogenesis as proposed by Zhang et al. (2010) includes direct DNA damage to cells in bone marrow or damage to circulating peripheral cells. These proposed mechanisms would require transport of formaldehyde from the portal of entry in a reactive form and concentrations present at the target tissue significantly greater than those endogenously present. The evidence does not support such transport.

Lack of evidence that exogenous formaldehyde is systemically absorbed

At low air concentrations of formaldehyde, transport of free formaldehyde through the mucus layer to the epithelial tissue of the respiratory tract and subsequent systemic transport are not expected (Priha et al. 1996).

Any "free" formaldehyde systemically would be vanishingly small due to the chemical/physical properties of formaldehyde; rapid metabolism to formate, carbon dioxide and water; and efficient

[1] A detailed discussion of these issues is presented in ENVIRON's August 31, 2010 comments on the USEPA's Draft IRIS Toxicological Review of Formaldehyde-Inhalation Assessment.

biochemical mechanisms for homeostatic control of tissue levels (Priha et al. 1996; Heck and Casanova 2004).

Concentrations of formaldehyde in blood before and after exposure to inhaled formaldehyde were indistinguishable in both humans and nonhuman primates (Casanova et al. 1988; Heck et al. 1985; Heck and Casanova 2004).

Predicted blood concentrations from exogenous formaldehyde are insignificant compared to endogenous formaldehyde production.

The failure of exogenous formaldehyde to increase endogenous formaldehyde concentrations in blood is predictable (Heck and Casanova 2004). Based upon inhalation of 2 ppm of exogenous formaldehyde for 8 hours by an adult man, and assuming 7% available for distribution (ignoring metabolism and binding of the absorbed formaldehyde) and distributed in total body water, the maximum blood concentration estimated would be 0.001 mM compared to a normal endogenously-generated concentration of 0.1mM (Heck and Casanova 2004). The equilibrium constant between formaldehyde and its metabolite, methanediol, indicates that less than 0.1% of formaldehyde is in an unhydrated, "free" or reactive" form (Priha et al. 1996).

Using a mathematical model describing absorption and removal of inhaled exogenous formaldehyde from nasal tissues in humans, the concentration of formaldehyde in respiratory tract mucus and epithelium is estimated to reach steady-state within seconds of exposure. The increase in formaldehyde concentration in blood is predicted to be insignificant compared to that from endogenously produced formaldehyde (Franks 2005).

Lack of evidence that exogenous formaldehyde reaches the bone marrow.

No detectable protein adducts or DNA-protein adducts, resulting from exogenous formaldehyde, were found in the bone marrow of metabolically competent or glutathione-depleted (metabolically inhibited) rats or monkeys (Casanova-Schmitz et al. 1984; Heck and Casanova 2004).

No detectable DNA adducts due to exogenous formaldehyde were found in the liver, spleen or bone marrow of rats exposed to 10 ppm formaldehyde; however, adducts from endogenous formaldehyde was measured in all tissues examined, and adducts from both endogenous and exogenous formaldehyde were measured in nasal tissues (Lu et al. 2010).

B. Formaldehyde Lacks the Same Patterns of Toxicity as Other Leukemogens

Despite possible differences in MOA, known leukemogens (i.e. ionizing radiation, benzene, cancer chemotherapeutic agents) produce hematotoxicity and lymphohematopoietic neoplasia in humans with concordance between animals and humans. However, there is a **lack of evidence for a causal association between formaldehyde exposure and either hematotoxicity or myeloid leukemia in epidemiological or animal toxicity studies**

Lack of evidence for a causal association between formaldehyde and hematotoxicity, e.g., pancytopenia.

Zhang et al. (2010) reported decreases in blood cell types in exposed compared to non-exposed workers, and the authors characterized these decreases as evidence of hematotoxicity, citing other

studies as support for this observation.[2] All numerical values in the Zhang et al. (2010) study for the blood cell types in both exposed and non-exposed individuals were within normal limits for Chinese populations (Arumanayagam et al. 1987; Kam et al. 1996; Chng et al. 2004; Grant 1969) and for worldwide populations (University of Texas Southwestern Medical Center 2010; King Saud University 2007; Medical Council of Canada 2010; Bloodbook.com 2007). In addition, reductions in WBC counts reported by Tong et al. (2007) and Qian et al. (1988) were within the normal range of WBC values for Chinese populations, studies by Tang and Zhang (2003), Xu et al. (2007) and Feng et al. (1996) reported no significant impact on WBC counts; studies by Yang (2007) and Cheng et al. (2004) reported incidences of personnel with "relatively low" (not defined) WBC counts; and Kuo et al. (1997) reported a correlation between decreases in WBC and formaldehyde, although no actual blood count data were provided and no significant correlation with any decreases in any other blood cell types was found.

No hematotoxic effects have been reported in any animal studies involving exposures to formaldehyde by either inhalation or oral routes at high concentrations for both acute and chronic durations (Appelman et al. 1988; Dean et al. 1984; Johannsen et al. 1986; Kamata et al. 1997; Kerns et al. 1983; Til et al. 1988, 1989; Tobe et al. 1989; Vargova et al. 1993; Woutersen et al. 1987).

No evidence was presented in the Zhang et al. (2010) paper that changes in either blood cell counts, or in any other reported endpoints, were correlated with formaldehyde concentrations in the workplace.

Lack of compelling evidence of a causal association between formaldehyde and myeloid leukemia in either epidemiological studies or toxicity studies in rodents.

The vast majority of the epidemiological studies have not reported a statistically significant association between formaldehyde exposure and the observed incidences of or deaths from leukemia[3]. No significant increase in mortality from myeloid leukemia was seen in the Beane Freeman et al. (2009) study for any dose-metric evaluated. Although Hauptmann et al. (2009) reported an increase in myeloid leukemia, when the number of embalmings or peak formaldehyde exposures was used as the measure of "exposure," questions remain about statistical analyses across categories and the completeness of exposure data[4].

No evidence of the development of leukemia was reported in animals exposed to formaldehyde by oral (Til et al. 1989) or inhalation routes (Swenberg et al. 1981; Kerns et al. 1983; Battelle 1981). Moreover, questions have arisen, as stated in USEPA's Draft IRIS Assessment, about survival in the high dose groups in mice and rats. Battelle (1981) applied the Tarone's extension to the Cox log-rank test (Tarone 1975), and reported a significant increase in leukemia in high dose female rats (p=0.056). However, this test is appropriate only when effects develop early and quickly (McKnight 1988). Moreover, the study authors did not report this as a significant finding (Battelle 1981; Swenberg et al. 1980; Kerns et al. 1983). When survival-adjusted statistical tests currently used by the National Toxicology Program, to include the Cochran-Armitage and Poly3 tests (Bailer and Portier 1988), are applied to the individual animal data,

---

[2] A critique of the Zhang et al. (2010) study has been submitted to this NAS Committee by Drs. Albertini, Irons, Shipp and Thirman.

[3] Drs. Cole, Mandel, Marsh and Mundt, have submitted a critique of the primary epidemiological studies to this NAS Committee.

[4] A number of uncertainties exist regarding the exposure history of subjects and these uncertainties raise questions about the validity of the conclusions reported by the authors. The authors note that a major issue was missing data on work histories that then had to be imputed from other data; that data were missing for up to 50% of the subjects in key categories, such as number of embalmings; that the method used to estimate peak exposure was not validated; and that a sensitivity analysis clearly demonstrated that, when analyses were limited to subjects for whom more than 70% of work histories were known, the association of formaldehyde exposure and critical categories, such as number of embalmings, no longer was statistically significant.

the incidence of leukemia in female rats or lymphoma in mice was not statistically significant. No significant increases were seen in the main oral study (Til et al. 1989) in which survival from intercurrent mortality was absent, thus reinforcing the conclusion that formaldehyde does not produce leukemia in experimental animals.

C. Lack of Evidence for Proposed Modes of Action for Leukemia

The proposed MOAs reported in the USEPA Draft Assessment rely heavily on MOAs hypothesized by Zhang et al. (2010). All of the mechanisms hypothesized by Zhang et al. (2010) depend on formaldehyde, or a formaldehyde-derived reactive metabolite, either (1) reacting directly with the bone marrow (direct genotoxicity), or (2) reacting with the DNA of circulating stem cells or progenitor cells at the portal of entry which cells then return to the bone marrow and result in a mutation and clonal expansion, finally resulting in leukemia (Zhang et al. 2009; DeVoney et al. 2006). There is no evidence nor any empirical data to support that these proposed MOAs actually occur following humans' inhalation of formaldehyde.

Lack of evidence for a direct genotoxic mode of action in bone marrow

Production of a direct genotoxic effect is predicated on evidence that a compound binds to critical intracellular macromolecules, such as key proteins or DNA, in target tissues. As noted above, there is no evidence that formaldehyde does either.

To the contrary, formaldehyde does not form either DNA:protein crosslinks (Casanova-Schmitz et al. 1984; Heck and Casanova 2004) or DNA adducts (Lu et al. 2010), in bone marrow. The results of the Lu et al. study demonstrates that neither inhaled formaldehyde nor methanediol reaches sites distant to the portal of entry. As the USEPA Draft Assessment itself says (Section 4.3.4.1), "Despite formaldehyde's reactivity and mutagenicity in isolated mammalian cells, clear evidence of mutagenicity does not emerge from animal bioassays." Indeed, the highest quality *in vivo* genotoxicity studies in animals do not show any evidence of genotoxic effects in tissues distant from the point of contact (Speit et al. 2009). The weight-of-evidence conclusion from these studies is that exogenous formaldehyde is not a direct genotoxic agent at sites distant from the point of exposure, in particular the bone marrow.

Lack of Evidence for Direct Effects in Circulating Cells or Progenitor Cells at the Portal of Entry

No consistent statistically significant relationship between formaldehyde exposure and chromosomal aberrations, sister chromatid exchanges, or micronucleated cells have been seen in any *in vivo* tests in animals. The USEPA Draft Assessment cites several studies in humans that purport to show genotoxic effects in tissues (such as lymphocytes) distant from the point of first exposure. However, these studies suffer from serious limitations that render it impossible to attribute real genotoxic effects to formaldehyde exposure. These limitations include uncertainties regarding exposure, a lack of control for potential confounders, and insufficient details of experimental methods and results (He et al. 1998; Shaham et al. 1997, 2002; Yager et al. 1986; Ye et al. 2005). **Importantly, the methods used do not differentiate between formaldehyde of endogenous and exogenous origin.** Importantly, no association between formaldehyde exposure and these chromosomal changes were reported in other human studies (Bauchinger and Schmid 1985; Chebotarev et al. 1986; Pala et al. 2008; Suruda et al. 1993; Thomson et al. 1984; Ying et al. 1999).

In addition, the presence and/or frequency of chromosomal aberrations in the peripheral blood are not validated markers of specific types of cancer. In Bonassi *et al.* (2008), which includes the genetic screening in 22,358 ***cancer-free*** individuals with follow-up for an average of 10 years, no significant

association between cancers of the lymphohematopoietic system and the frequency of chromosomal aberrations was reported. **Moreover, there is no evidence that circulating hematopoietic stem cells return to bone marrow during homeostasis (McKinney-Freeman and Goodell (2004).**

The Draft IRIS Assessment states that Zhang et al. (2010) tested the hypothesis that exogenous formaldehyde may damage circulating myeloid leukemia progenitor cells. However, there are numerous limitations in relying upon Zhang et al. (2010). A Freedom of Information Act (FOIA) request was used to obtain the data from NCI concerning the Chinese workers who were included in the Zhang et al. (2010) analysis.[5] Additional analyses of the aneusomy data were performed[6] using the Zhang et al. (2010) statistical tests but restricted to subjects for whom greater than 80 cells were examined. No significant differences in exposed compared to non-exposed existed for either the number of chromosomes with monosomy 7 or trisomy 8 changes. Furthermore, use of Chinese medicine alone (without consideration of formaldehyde exposure) was significantly associated with these effects. Therefore, this study **may not be considered reliable and may not be used to confirm any causal relationship between formaldehyde and myeloid leukemia.**

D. Lack of Consideration of Endogenous Levels

Under the assumption that formaldehyde causes nasal tumors, Hodgkins lymphoma, and myeloid leukemia, USEPA (2010) conducted dose-response analyses for all three neoplasms combined, resulting in a unit risk factor (URF) of 8.1×10^{-2} per ppm. Based on this URF, the air concentration associated with a one-in-a-million risk (considered negligible by EPA policy) would be 1.23×10^{-5} ppm or 12.3 ppt. When compared to normal exhaled formaldehyde, with median concentrations ranging from 1 to 10 ppb, as reported by Cap et al. 2008, and Wang et al. 2008, 12.3 ppt is orders of magnitude below levels of formaldehyde anticipated to be exhaled as a result of normal biological processes.

E. Lack of Overall Strength of the Evidence Regarding the Biological Plausibility of an Association with Leukemia

Formaldehyde is rapidly metabolized and highly reactive and, because it is an endogenous compound, a detectable change in the natural background levels would be necessary to result in the potential for adverse effects. Existing mechanistic data for formaldehyde provide no evidence that exogenous formaldehyde will be transported from the point of contact to distant sites, or that formaldehyde can significantly impact endogenous levels. However, these data do provide evidence that formaldehyde does not affect the relevant target cells (bone marrow or peripheral blood) for leukemia. In sum, there is no evidentiary basis for any of the proposed MOAs hypothesized by Zhang et al. (2010).

[5] The numerous limitations of the Zhang et al. (2010) study are discussed in another submission to the NAS Committee, as noted above, and were described in ENVIRON International Corporation's comments on the Draft IRIS Assessment submitted August 31, 2010 (Environ 2010).

[6] Dr Annette Bachand of Colorado State University conducted additional statistical analysis of the Zhang et al. (2010) data.

In conclusion, in evaluating the available epidemiological, toxicological, and mechanistic data for formaldehyde, the weight–of- evidence does not support a finding of a causal association between formaldehyde and myeloid leukemia.

Sincerely,

Annette M. Shipp, PhD
Principal
ENVIRON International Corporation
Monroe, LA

Robinan Gentry, PhD
Senior Science Manager/Toxicologist
ENVIRON International Corporation
Monroe, LA

Duncan Turnbull, DPhil
Senior Science Manager
ENVIRON International Corporation
Arlington, VA

REFERENCES

Appelman, LM; Woutersen, RA; Zwart, A; et al. (1988) One-year inhalation toxicity study of formaldehyde in male rats with a damaged or undamaged nasal mucosa. J Appl Toxicol 8:85–90.

Arumanayagam, M; Lam, YM; Swaminathan, R; et al. (1987). Blood cell values in healthy Hong Kong Chinese adults. Clinical and Laboratory Haematology 9(3):263-269.

Bailer, AJ; Portier, CJ. (1988) Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. Biometrics 44:679-682.

Battelle Columbus Laboratories (Battelle). (1981) Final report on a chronic inhalation toxicology study in rats and mice exposed to formaldehyde. Prepared by Battelle Columbus Laboratories, Columbus, OH for the Chemical Industry Institute of Toxicology (CIIT). Research Triangle Park, NC; CIIT Docket # 10922.

Bauchinger, M; Schmid, E. (1985) Cytogenetic effects in lymphocytes of formaldehyde workers of a paper factory. Mutat Res 158:195–199.

Beane-Freeman, LE; Blair, A; Lubin, JH; et al. (2009) Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute cohort. Journal of the National Cancer Institute 101(10):751-761.

Bloodbook.com. (2007). Blood test results – Normal ranges. http://www.bloodbook.com/ranges.html. Accessed on 2/2/2010.

Bonassi, S; Norppa, H; Ceppi, M; et al. 2008. Chromosomal aberration frequency in lymphocytes predicts the risk of cancer: results from a pooled cohort study of 22 358 subjects in 11 countries. Carcinogenesis 29(6): 1178-1183.

Cáp P, Dryahina K, Pehal F, et al. (2008) Selected ion flow tube mass spectrometry of exhaled breath condensate headspace. Rapid Commun Mass Spectrom. 22(18):2844–2850.

Casanova M, Heck HD, Everitt JI, et al. (1988) Formaldehyde concentrations in the blood of rhesus monkeys after inhalation exposure. Food Chem Toxicol 26:715–716.

Casanova-Schmitz, M; Starr, TB; Heck, HD. (1984) Differentiation between metabolic incorporation and covalent binding in the labeling of macromolecules in the rat nasal mucosa and bone marrow by inhaled [14C]- and [3H]-formaldehyde. Toxicol Appl Pharmacol 76:26–44.

Chebotarev, AN; Titenko, NV; Selezneva, TG, et al. (1986) [Comparison of chromosome aberrations, sister chromatid exchanges and unscheduled DNA synthesis in the evaluation of the mutagenicity of environmental factors]. Tsitol Genet 20:109-115.

Cheng, Z; Li, Y; Liang, B; et al. (2004) Investigation of formaldehyde levels and health of personnel in clinical pathology. J Bengbu Med Coll. 29(3):266-267.

Chng, W; Tan, G; Kuperan, P. (2004). Establishment of adult peripheral blood lymphocyte subset reference range for an Asian population by single-platform flow cytometry: Influence of age, sex,

and race and comparison with other published studies. Clinical and Diagnostic Laboratory Immunology 11(1):168-173.

Dean, JH; Lauer, LD; House, RV; et al. (1984) Studies of immune function and host resistance in B6C3F1 mice exposed to formaldehyde. Toxicol Appl Pharmacol 72:519–529.

DeVoney, D; Jinot, J; Keshava, C; et al. (2006) In a hypothesized mode of action in support of biological plausibility of formaldehyde-induced lymphohematopoietic malignancies. Society for Risk Analysis (Abstract).

Grant, J. (1969). Haematological indices in healthy Chinese (A survey of 3,983 in Hong Kong). Singapore Medical Journal. 10(3) 211-213.

Feng, Y; Wang, W; Jiang, Z; et al. (1996) Health status of wood workers exposed to formaldehyde. Anhui J Prev Med 2(2):99-100.

Franks, SJ. (2005) A mathematical model for the absorption and metabolism of formaldehyde vapor by humans. Toxicology and Applied Pharmacology 206(3): 309-320.

Hauptmann, M; Stewart, P; Lubin, J; et al. (2009) Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. JNCI 101:1-13.

He, JL; Jin, LF; Jin, HY. (1998) Detection of cytogenetic effects in peripheral lymphocytes of students exposed to formaldehyde with cytokinesis-blocked micronucleus assay. Biomed Environ Sci 11:87–92.

Heck, HD, Casanova, M. (2004) The implausibility of leukemia induction by formaldehyde: A critical review of the biological evidence on distant-site toxicity. Regul Toxicol Pharmacol 40:92–106.

Heck, HD; Casanova-Schmitz, M; Dodd, PB; et al. (1985) Formaldehyde (CH2O) concentrations in the blood of humans and Fischer-344 rats exposed to CH2O under controlled conditions. Am Ind Hyg Assoc J 46:1–3.

Johannsen, FR; Levinskas, GJ; Tegeris, AS. (1986) Effects of formaldehyde in the rat and dog following oral exposure. Toxicol Lett 30:1–6.

Kam, KM; Leung, WL; Kwok, MY; et al. (1996). Lymphocyte subpopulation reference ranges for monitoring human immunodeficiency virus-infected Chinese adults. Clinical and Diagnostic Laboratory Immunology. 3(3) 326-330.

Kamata, E; Nakadate, M; Uchida, O; et al. (1997) Results of a 28-month chronic inhalation toxicity study of formaldehyde in male Fisher-344 rats. J Toxicol Sci 22:239–254.

Kerns, WD; Pavkov, KL; Donofrio, DJ; et al. (1983) Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. Cancer Res 43:4382–4392.

King Saud University. (2007). Normal lab values. College of Pharmacy. http://colleges.ksu.edu.sa/CollegeofPharmacy/Drug%20and%20Poison%20Information%20Center/English%20information/ICMLabValuesVer.doc. Accessed on 2/2/2010.

Kuo, H; Jian, G; Chen, C; et al. (1997) White blood cell count as an indicator of formaldehyde exposure. Bull Environ Contam Toxicol 59(2):261-267.

Lu, K; Collins, B; Ru, H; et al. (2010) Distribution of DNA adducts caused by inhaled formaldehyde is consistent with induction of nasal carcinoma but not leukemia. Toxicological Sciences 116(2):441-451.

McKinney-Freeman, S; Goodnell, MA. (2004) Circulating hematopoietic stem cells do not efficiently home to bone marrow during homeostasis. Exp Hematol 32(9):868-876.

Medical Council of Canada. (2010). Clinical laboratory tests normal Values. http://www.mcc.ca/objectives_online/objectives.pl?lang=english&loc=values. Accessed 2/2/1010.

Pala, M; Ugolini, D; Ceppi, M; et al. (2008) Occupational exposure to formaldehyde and biological monitoring of Research Institute workers. Cancer Detection and Prevention 32(2): 121-126.

Priha, E; Liesivuori, J; Santa, H; et al. (1996) Reactions of hydrated formaldehyde in nasal mucus. Chemosphere 32:1077–1082.

Qian, RJ; Zhang, PH; Duang, TL; et al. (1988) Investigation on occupational hazards of formaldehyde exposure (abstract) Ind Hyg and Occup Dis 14(2):101.

Shaham, J; Gurvich, R; Kaufman, Z. (2002) Sister chromatid exchange in pathology staff occupationally exposed to formaldehyde. Mutat Res 514:115–123.

Shaham, J; Bomstein, Y; Melzer, A; et al. (1997) DNA-protein crosslinks and sister chromatid exchanges as biomarkers of exposure to formaldehyde. Int J Occup Environ Health 3:95–104.

Speit, G; Zeller, J; Schmid, O, et al. (2009) Inhalation of formaldehyde does not induce systemic genotoxic effects in rats. Mutat Res 677(1-2):76-85.

Suruda, A; Schulte, P; Boeniger, M; et al. (1993) Cytogenetic effects of formaldehyde exposure in students of mortuary science. Cancer Epidemiol Biomarkers Prev 2:453–460.

Swenberg, JA; Kerns, WD; Mitchell, RI; et al. (1980) Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. Cancer Res 40:3398–3402.

Tang, LX; Zhang, YS (2003) Heath Investigation on workers exposed to formaldehyde. Occup Health 19(7):34-35.

Tarone, RE. (1975) Tests for trend in life table analysis. Biometrika 62:679-682.

Thomson, EJ; Shackleton, S; Harrington, JM. (1984) Chromosome aberrations and sister-chromatid exchange frequencies in pathology staff occupationally exposed to formaldehyde. Mutat Res 141:89–93.

Til, HP; Woutersen, RA; Feron, VJ; et al. (1989) Two-year drinking-water study of formaldehyde in rats. Food Chem Toxicol 27:77–87.

Til, HP; Woutersen, RA; Feron, VJ; et al. (1988) Evaluation of the oral toxicity of acetaldehyde and formaldehyde in a 4-week drinking-water study in rats. Food Chem Toxicol 26:447–452.

Tobe, M; Naito, K; Kurokawa, Y. (1989) Chronic toxicity study on formaldehyde administered orally to rats. Toxicology 56:79–86.

Tong, ZM; Zhu, SX; et al. (2007) Effect of formaldehyde on blood component and blood biochemistry of exposed workers. Chin J Ind Med 20(6):409-410.

University of Texas Southwestern Medical Center. (2010). Normal reference range table. Department of Pathology. http://pathcuric1.swmed.edu/pathdemo/nrrt.htm. Accessed on 2/2/2010.

US Environmental Protection Agency (USEPA). (2010) Toxicological Review of Formaldehyde – Inhalation Assessment. Washington, DC, EPA/635/R-10/002A, June 2, 2010.

Vargová, M; Wagnerova, J; Liskova, A; et al. (1993) Subacute immunotoxicity study of formaldehyde in male rats. Drug and Chemical Toxicology 16(3):255-75.

Wang TS, Pysanenko A, Dryahina K, Španěl P, Smith D. (2008) Analysis of breath, exhaled via the mouth and nose, and the air in the oral cavity. J. Breath Res. 2:1-13.

Woutersen, RA; Appelman, LM; Wilmer, JW; et al. (1987) Subchronic (13-week) inhalation toxicity study of formaldehyde in rats. J Appl Toxicol 7:43–49.

Xu, SY; Yi, GL; et al. (2007) Hygiene investigation of the effect of formaldehyde on the workers' health. Occup Health 23(7):491-492.

Yager, JW; Cohn, KL; Spear, RC; et al. (1986) Sister-chromatid exchanges in lymphocytes of anatomy students exposed to formaldehyde-embalming solution. Mutat Res 174:135–139.

Yang, YJ. (2007) Analysis of indoor air formaldehyde pollution in 20 newly remodeled rooms in Shenyang. China Sci Technol 16:16-21.

Ye, X; Yan, W; Xie, H; et al. (2005) Cytogenetic analysis of nasal mucosa cells and lymphocytes from high-level long-term formaldehyde exposed workers and low-level short-term exposed waiters. Mutat Res 588:22–27.

Ying, CJ; Ye, XL; Xie, H; et al. (1999) Lymphocyte subsets and sister-chromatid exchanges in the students exposed to formaldehyde vapor. Biomed Environ Sci 12:88–94.

Zhang, L; Tang, X; Rothman, N; et al. (2010) Occupational exposure to formaldehyde, hematotoxicity, and leukemia-specific chromosome changes in cultured myeloid progenitor cells. Cancer Epidemiology, Biomarkers & Prevention 19(1):80-88.

Zhang, L; Steinmaus, C; Eastmond, DA; et al. (2009) Formaldehyde exposure and leukemia: A new meta-analysis and potential mechanisms. Mutation Research 681(2-3):150-168.